Add the following new claims.

69. (New) The nucleic acid of claim 17, wherein said nucleic acid is a nematode nucleic acid.

Support for the Amendments

The claims have been amended to more precisely define the invention with respect to the nucleic acids being claimed. Support for new claim 69 can be found at page 16, lines 17-35. No new matter is added by these amendments.

REMARKS

Summary of the Invention and the Office Action

The invention features wild-type and mutant *ced-3* nucleic acids. The *ced-3* gene is required for the onset of programmed cell death in *C. elegans*. Such nucleic acids that increase or decrease cell death are useful, for example, in the treatment of disorders and conditions characterized by aberrant increases or decreases in cell death, including cancer, neural and muscular degenerative diseases, stroke, traumatic brain injury, myocardial infarction, viral (e.g., HIV) infections as well as other types of pathogenic infections, and cell death associated with normal aging and hair loss.

Claims 1-4, 8-15, 17, 18, 21, and 36 were examined in this case. All claims stand rejected. The present response cancels claims 2, 9, 10, and 11, amends claims 1, 3, 8, 17, 21, and 36, and adds new claim 69. Each of the objections and rejections levied in the Office Action is addressed individually below.

Amendments

The Examiner notes that claims 9-11, 22, 25-27, 33, 35, and 40 have been canceled according to the Amendment of March 2, 2000 (Paper No. 12). However, the Office Action Summary indicates that claims 9-11 are still pending. Applicants request that the cancellation of claims 9-11 (as requested in the Amendment of March 2, 2000) be confirmed it the next Office Action.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 8, 15, 17, 18, 21, and 36 stand rejected for lack of enablement. The Examiner acknowledges that the specification is enabling for: the *ced-3* gene disclosed in SEQ ID NO: 18; the DNA encoding the amino acid sequence of SEQ ID NO: 19; the *ced-3* mutants listed in Table 3, page 62, of the specification; and probes and primers designed on the basis of these sequences. However, the Examiner states that the specification does not reasonably provide enablement for isolated DNAs for any and all isolated *ced-3* nucleic acids, any and all nucleic acids, probes and primers, structurally

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related, functionally related, or structurally and functionally related to *ced-3*, which antagonize the activity of functional cell death genes.

In the interest of obtaining allowance of this case, claims 1, 8, 17, 21, and 36 have been amended to specifically recite relation of the claimed sequence to "SEQ ID NO: 18." Claim 15 depends from claim 8 and claim 18 depends from claim 17, thus claims 15 and 18 also incorporate this mutation. Applicants reserve the right to pursue broad claims in a future application.

Claim 1 is now directed to isolated and purified nucleic acids encoding the *ced-3* gene of SEQ ID NO: 18 and claim 21 is directed to probes and primers that include all or a portion of the *ced-3* nucleic acid of SEQ ID NO: 18. Claim 17 recites isolated and purified nucleic acids that are structurally and functionally related to the *ced-3* nucleic acid of SEQ ID NO: 18, and claims 8 and 36 similarly relate to isolated and purified *ced-3* nucleic acid sequences that have a mutation in the sequence of SEQ ID NO: 18. In claim 8, the mutation affects the ability of the mutated *ced-3* gene to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay. In claim 36, the mutation affects the ability of the mutated nucleic acid to complement *ced-3* or *ced-4* mutations in an *in vivo* or *in vitro* bioassay and results from a) inactivation of the *ced-3* nucleic acid; b) constitutive activation of the *ced-3* nucleic acid; or c) production of a mutated *ced-3* nucleic acid which does not cause cell death and which antagonizes the activity of functioning cell death genes.

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Applicants assert that since claims 1 and 21 now specifically recite SEQ ID NO: 18 these claims satisfy the requirements of 35 U.S.C. § 112, first paragraph (see pages 10-13 of the specification, Figure 4, and SEQ ID NO: 18). Therefore, the following arguments are directed to claims 8, 15, 17, 18, and 36.

Isolation of ced-3 Genes

Applicants argue that those of ordinary skill in the art would recognize that additional *ced-3* nucleic acids may be routinely isolated using the nucleic acid of SEQ ID NO: 18, or a portion thereof. In fact, additional *ced-3* genes and mutants thereof can be identified by simply following the repeatable process taught by the specification. Specifically, the specification teaches that one may 1) isolate a nucleic acid encoding at least a portion of a *ced-3* gene or *ced-3* gene mutant based on the nucleic acid sequence of SEQ ID NO: 18; and 2) test the function of the candidate *ced-3* gene or *ced-3* gene mutant in an *in vivo* or *in vitro* bioassay.

To complete step 1, it would be obvious to the skilled artisan to simply use the probes and primers of claim 21 to clone additional *ced-3* genes using methods standard in the art. The specification clearly provides guidance on how to isolate genes and gene mutants based on the sequence of a known gene (see, e.g., page 15, line 16 to page 17, line 14 and page 45, lines 8-10).

Alternatively, the specification teaches that one may "initially probe animals

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which are taxonomically closely related to the source of the probes, for example, probing other worms with a *ced-3* [. . .] probe" (page 15, line 33 to page 16, line 2). Indeed, the first step of identifying *ced-3* genes in other worms had been completed at the time of the invention. Two additional *ced-3* genes from other *Caenorhabditis* species, *C. briggsae* and *C. vulgaris*, are described in the specification at page 16, lines 28-30 and in Example 2. As described in the specification (page 16, lines 5-7), this information may be used to next identify additional *ced-3* genes from less closely related species (e.g., mammalian species).

With respect to the identification of mutant *ced-3* genes, it would be routine for the skilled artisan, having the knowledge of the nucleic acid sequence of SEQ ID NO:18 combined with an analysis of the regions of the *ced-3* nucleic acid sequence that are conserved between *ced-3* genes and the function of the *ced-3* gene, to generate mutants that affect the ability of *ced-3* to complement *ced-3* or *ced-4* in an *in vivo* or *in vitro* bioassay (e.g., as in claims 8 and 36). As noted above, several *Caenorhabditis ced-3* genes had already been identified at the time of the invention. These conserved regions are likely to be important for the activity of the *ced-3* protein (page 16, lines 19-25) and could easily be targeted for mutational analysis.

Alternatively, as stated at page 17, lines 1-2, "functionally important regions can also be identified by mutagenesis." The specification teaches that "mutations and other alterations can be accomplished using known methods, such as *in vivo* and *in vitro*

mutagenesis (see, e.g., Ausubel et al. (eds.), Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley-Interscience, New York)" (page 17, lines 10-14). The *ced-3* mutants may then, of course, be tested to determine whether the mutations affect the ability of the *ced-3* nucleic acid to complement *ced-3* or *ced-4* in an *in vivo* or *in vitro* bioassay, as set forth in the claims.

Indeed, inactivating mutations of *ced-3* have already been identified within a region near the COOH-terminus (Figure 5B), suggesting that this region is a functionally important domain of the Ced-3 protein, as described at page 17, lines 2-9. The fact that mutants of the Ced-3 protein had already been identified at the time of the invention further supports the assertion that the identification of additional *ced-3* mutants is well within the ability of the skilled artisan and well within the scope of the present claims.

Function of ced-3 genes

In order to accomplish testing the function of the putative *ced-3* gene or *ced-3* gene mutant in an *in vivo* or *in vitro* bioassay (step 2, above) one would merely use a candidate *ced-3* nucleic acid sequence, e.g., a sequence related to SEQ ID NO: 18 or a mutant of SEQ ID NO: 18, in an *in vivo* or *in vitro* bioassay. Specific *in vivo* and *in vitro* bioassays are described at page 17, line 15 to page 20, line 4. A working example of one such bioassay, an *in vivo* rescue assay, is provided in Example 2, page 52, line 11 to page 54, line 24. Thus, the specification explicitly provides a means for assaying the activity

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of *ced-3* and demonstrates successful use of the assay to verify the function of a *ced-3* gene. In light of these teachings, it would be straightforward for one of ordinary skill to 1) isolate a nucleic acid encoding at least a portion of a *ced-3* gene or *ced-3* gene mutant, and 2) test the function of the candidate *ced-3* gene or *ced-3* gene mutant (i.e., the ability to complement *ced-3* or *ced-4*) in an *in vivo* or *in vitro* bioassay.

The Examiner acknowledges on page 3 of the Office Action that "the method to isolate said nucleic acids may be routine." However, the Examiner asserts that if an artisan does not know whether function, structure, or other characteristics of all the claimed nucleic acids is the same, the artisan would not know how to make and use the nucleic acids. This argument does not reflect what is claimed.

The specification describes exactly how an artisan would routinely test whether the function of the claimed nucleic acids are the same. Furthermore, the claims set forth that all *ced-3* nucleic acids must have these characteristics. The claims specifically recite the function of the *ced-3* nucleic acid as having the ability to complement *ced-3* and *ced-4* mutations in an *in vivo* or *in vitro* bioassay, which are clearly taught by the specification and are standard in the art. Applicants wish to point out that if it is routine to isolate *ced-3* nucleic acids (as stated by the Examiner), and if it is routine to test the function of such a nucleic acid in an *in vitro* or *in vivo* bioassay (for their ability to complement *ced-3* or *ced-4*), and furthermore, if it is expected that at least some of these nucleic acids will be *ced-3* nucleic acids or mutant *ced-3* nucleic acids, then the presently

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claimed invention is clearly enabled. For example, once a *ced-3* nucleic acid is routinely identified, it may be simply subcloned into an expression vector and injected into a *ced-3* mutant nematode to "observe the effect of the transgene on the pattern of programmed cell deaths during development of the nematode" (page 18, lines 2-4 and page 53, lines 18-21). The *ced-3* gene is a gene that affects programmed cell death and assays to measure programmed cell death are standard in the art and provided in the specification, as described above.

Those skilled in the art will appreciate that the methods of identifying *ced-3* genes described above are applicable to the identification of *ced-3* genes in other organisms. For example, additional *ced-3* genes may be routinely isolated from other organisms using the sequence of *ced-3* and the functional characteristics of *ced-3* provided by the specification (e.g., by screening a mammalian cDNA library with the *ced-3* probes and primers of claim 21 and testing ability of the cloned cDNA to complement the *ced-3* phenotype). Another aspect of this teaching is that these characteristics are similarly applicable to the identification of mutant *ced-3* genes of other organisms, as described in the specification (page 15, lines 33-34).

In summary, having been provided with the both the nucleic acid sequence of the *ced-3* gene, the specific function of the *ced-3* gene, and an assay by which to test the function of the *ced-3* gene, one of ordinary skill in the art could easily and routinely identify additional *ced-3* genes that are related to SEQ ID NO: 18 and are able to

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complement *ced-3* or *ced-4* in an *in vivo* or *in vitro* bioassay. Similarly, mutations that affect the ability of *ced-3* to complement *ced-3* or *ced-4* could also be identified. In light of these teachings, Applicants submit that the specification fully enables claims of the present scope, as amended herein.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 8, 15, 17, 18, 21, and 36 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner refers to the previous Office Action of August 31, 1999, where the Examiner states that a representative number of species have not been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence) and there is no disclosure about the extent or type of sequence or functional relationship. Applicants disagree.

As pointed out above, the claims have been amended to recite a relationship between the claimed sequences and SEQ ID NO: 18. Furthermore, the specification defines "functionally related genes" as those "which have similar activity to that of *ced-3*... in that they cause cell death" (page 13, lines 21-22), and further that "such genes can be identified by their ability to complement *ced-3*... mutations in bioassays" (page 13,

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lines 22-25). Specific *in vivo* and *in vitro* bioassays for measuring the activity of *ced-3* are described at page 17, line 15 to page 20, line 4 and in Example 2, at page 52, line 11 to page 54, line 24. Moreover, Applicants point out that the specification demonstrates the cloning of several additional species of the *ced-3* gene that are related to SEQ ID NO: 18, specifically, three *ced-3* genes from *C. elegans*, *C. briggsae,* and *C. vulgaris* (page 11, lines line 29 to page 12, line 2).

With respect to *ced-3* mutants, on page 17, lines 1-14, the specification states that "functionally important regions can also be identified by mutagenesis." The specification demonstrates that inactivating mutations of *ced-3* were found to cluster within a region near the COOH-terminus (Figure 5B) and suggests that this region is a functionally important domain of the Ced-3 protein. Furthermore, on page 17, lines 1-14, the specification refers the skilled artisan to a common molecular biological handbook that includes methods of mutagenesis for guidance on how to perform *in vivo* and *in vitro* mutagenesis. Moreover, the specification demonstrates identification of a number of mutants of the *ced-3* gene (see, Example 2 and Table 3). The skilled artisan could simply repeat the methods demonstrated in Example 2 and sequence any EMS-induced *ced-3* alleles in order to identify mutants of the *ced-3* gene. Based on these teachings, Applicants were clearly in possession of the invention as set forth in claims 1, 4, 8, 15, 17, and 18.

Thus, in view of the above, Applicants assert that the specification provides a

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written description sufficient to meet the standards set forth under 35 U.S.C. § 112, first paragraph, for the claims, as amended herein.

Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1, 8, 17, and 21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that it is unclear what constitutes "a serine rich region." In response, this phrase has been deleted from claims 1, 8, 17 and 21 and this rejection should be withdrawn.

Rejections under 35 U.S.C. §102(b)

The Examiner asserts that claims 1, 8, 15, 17, 18, 21, and 36 are anticipated by Yuan (1990) on the assertion that Yuan teaches the cloning of *ced-3* in Chapter 3. Specifically, the Examiner asserts that Yuan teaches the mapping of *ced-3* and limits the *ced-3* gene to an interval of two cosmids. The Examiner further asserts that the clone was further characterized by digestion and bioassay and finally the subclone C48D1-28 was isolated, which still rescued *ced-3*. The Examiner further states that Yuan also teaches that the *ced-4* gene is related to the *ced-3* gene and therefore can be used for making probes in addition to teaching bioassays to isolate *ced-3* and *ced-4* genes.

Applicants assert that a *ced-3* nucleic acid that is isolated and purified is not the same as a *ced-3* nucleic acid on a cosmid, as set forth in Yuan. On a cosmid, the *ced-3*

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nucleic acid is flanked by other genes and nucleic acid sequences that flank the *ced-3* gene on the chromosome. In contrast, the *ced-3* gene of the invention as now claimed is isolated and purified and is not flanked by endogenous nucleic acid sequence. As defined in *Webster's Ninth New Collegiate Dictionary*, Merriam-Webster Inc., Publishers Springfield, Massachusetts, U.S.A., "isolated" means 'occurring alone or once." Similarly, the definition of "isolate" is "to set apart from others" or to separate from another substance so as to obtain pure or in a free state." In addition, the term "purify" is defined as "to free from undesirable elements." Therefore, an isolated and purified *ced-3* nucleic acid of SEQ ID NO: 18, as set forth in the claims, is a *ced-3* nucleic acid that is separated away from the endogenous nucleic acid sequences that flank the ced-3 gene in the chromosome of a cell.

The above interpretation of the claims is supported by current case law. As stated in *Gentry Gallery, Inc. v. Berkline Corp.*, (134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) "The proper construction of claims is based upon the claim language, the written description portion of the specification, the prosecution history, and if necessary to aid the court's understanding of the patent, extrinsic evidence." As set forth in *Markman v. Westview Instuments, Inc.*, (52 F.3d 967, 34 USPQ2d 1321 (Fed. Cir. 1995) (*in banc, aff'd*, 517 U.S. 370, 38 USPQ2d 1461 (1996) "Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises" [Emphasis Added].

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In conclusion, Applicants wish to point out that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" (MPEP § 2131). As stated in *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1986, "[It] is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention." The reference Yuan et al. is completely lacking of any teachings of an isolated or purified *ced-3* nucleic acid, as set forth in the claims (i.e., since the nucleic acid of Yuan et al. is flanked by its endogenous nucleic acid sequences). Therefore, Yuan et al. simply does not contain every element of the claimed invention, and is not anticipatory under 35 U.S.C. 102(b). Withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicants submit that in light of the above, the claims should now be in condition for allowance. Enclosed is a petition to extend the period for replying for 3 months, to and including November 23, 2000. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: November 17, 2000

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